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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/185,607	11/04/98	LEUNG S	018733/0875

HM12/0622

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EXAMINER	
HELMS,L	
ART UNIT	PAPER NUMBER
1642	12

DATE MAILED: 06/22/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant
09/185,607	Leung et al
Examiner	**Art Unit**
Larry R. Helms Ph.D.	1642

-- The MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *7 May 2001*

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 2, 4-19, and 21-55* is/are pending in the applica

4a) Of the above, claim(s) *15, 28, and 30-37* is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 2, 4-14, 16-19, 21-27, 29, and 38-55* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

1. Claims 1-2, 4-19, 21-55 are pending.

Claims 38-55 have been added.

Claims 1, 6, 8, 14, 16, 19, 20, 22, 23, 30, 33 have been amended.

2. Claims 15, 28, and 30-37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions. Election was made **without** traverse in Paper No. 12.

3. Claims 1-2, 4-14, 16-27, 29, and 38-55 are under examination.

4. The text of those sections of Title 35, U.S.C. Code not included in this Office Action can be found in a prior Office Action.

5. The following Office Action contains some NEW GROUNDS of rejections.

Rejections Withdrawn

6. The rejection of claims 1-14, 16-18 under 35 U.S.C. 112, second paragraph, for paragraph 6a and c in the previous Office action, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendments to the claims.

7. The rejection of claims 19, 21-22, 24-26, and 29 under 35 U.S.C. 102(b) as being anticipated by Sivam et al (WO 90/03401, published 4/5/90, IDS #5) is withdrawn in view of the amendments to the claims.

8. The rejection of claims 22-26 under 35 U.S.C. 102(b) as being anticipated by Leung et al (J. Of Immunology 154:5919-5926, 1995, IDS #5) is withdrawn in view of the amendment to the claims.

9. The rejection of claims 19-21 under 35 U.S.C. 103(a) as being unpatentable over Sivam et al (WO 90/03401) and further in view of Hansen et al (U.S. Patent 5,443,953, issued 8/22/95) is withdrawn in view of the amendments to the claims.

10. The rejection of claims 22-25 and 27 under 35 U.S.C. 103(a) as being unpatentable over Sivam et al (WO 90/03401) as applied to claims 22 and 25 above, and further in view of Li et al (Bioconjugate chem. 4:275-283, 1993) is withdrawn in view of the amendments to the claims.

11. The rejection of claims 22-26 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 5,443,953 is withdrawn in view of the amendments to the claims.

Response to Arguments

12. The rejection of claims 1, 4-14, 16-18 and newly submitted claims 38-39, 41-42, 44-45, 47-48, 50-51 and 55 under 35 U.S.C. 112, second paragraph, for paragraph 6b in the previous Office action, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained.

The response filed 5/7/01 has been carefully considered but is deemed not to be persuasive. The response states that the specification provides adequate definition and guidance

to skilled artisan and cites text at page 7, lines 5-11 as evidence thereof. In response to this argument, it is still unclear what "precursor" or "derivative" means. Since it is unclear how the "saccharide precursor" are to be derivatized or what a ketone derivative is in order to yield the class of derivatives referred to in the claims, there is no way for a person of skill in the art to ascribe a discrete and identifiable class of compounds to said phrase. Moreover, does the phrase "ketone derivative" mean an aldehyde? In addition, since the term "derivative" does not appear to be clearly defined in the specification, and the term can encompass many types of molecules. In addition, it is not clear what is meant by "saccharide precursor". Does the phrase mean a molecule that can be used in the biosynthetic pathway to a saccharide such as starch, carbon atoms, etc? In absence of a single defined art recognized meaning for the phrases and lacking a definition of the terms in the specification, one of skill in the art could not determine the metes and bounds of the claims.

13. The rejection of claims 1-2, 4-14, 16-19, 21-27, 29, and newly submitted claims 38, 41, 44, 47, 50, 53-55 under 35 U.S.C. 112, first paragraph, is maintained and made again.

The response filed 5/7/01 has been carefully considered but is deemed not to be persuasive. The response states "a total of five CH1 sites (HCN1-5) and five Cκ sites (KCN1-5) were designed and engineered in Example 2" and "these Cκ sites were not glycosylated" and "A skilled artisan also would be able to use ketone derivatives of saccharides and saccharide precursors other than N-levulinoyl mannosamine and N-levulinoyl frucose" and other antibodies

other than hLL2 can be used. In response to these arguments, as stated in the response not all engineered sites are glycosylated, therefore, one skill in the art would have to perform undue experimentation to determine which sites would get glycosylated. The response states that computer modeling can assist in the design of engineered glycosylation sites, however, this technique was used in the instant application for those sites in the Cκ sites and in the KCN1-5 sites these sites were not glycosylated. Thus, it would require undue experimentation to design glycosylation sites that do get glycosylated based on the specification alone. In addition, the specification does not enable any other "ketone derivatives of saccharides and saccharide precursors" other than N-levulinoyl mannosamine and N-levulinoyl frucose and it would require undue experimentation to determine which ketone derivatives (or how they are "derived") of saccharides and saccharide precursors other than N-levulinoyl mannosamine and N-levulinoyl frucose would work in the claimed method and result in a glycosylated antibody or antigen binding fragment. In response to the argument that other antibodies may be used, it is true that a glycosylation site was engineered at position 18 in MN14, however, the claims in the instant application are directed to antibodies with a reactive ketone group and as stated in the response not all sites are glycosylated in the hLL2 antibody, therefore, one skill in the art would conclude that not all antibodies will be glycosylated or glycosylated in all engineered sites in the CH1 or Vκ domain.

The following are some NEW GROUNDS of rejections

Claim Rejections - 35 USC § 112

14. Claims 39-40, 42-43, 45-46, 48-49, 51-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 39, 42, 45, 48, 51 recites the limitation "said antibody" in claims 38, 41, 44, 47, and 50 respectively. There is insufficient antecedent basis for this limitation in the claim. It is not clear if the "glycosylated antibody" produced by the method is selected from the group recited in the claim.

15. The claims 39-40, 42-43, 45-46, 48-49, and 51-52 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

a. It is unclear if a cell line which produces an antibody having the exact chemical identity of hLL2HCN1, hLL2HCN5, and hLL2Vκ-N are known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and

functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

b. For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species hLL2HCN1, hLL2HCN5, and hLL2Vκ-N. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

16. Claims 19-26 and 53-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shih et al (U. S. Patent 5,057,313, issued 10/15/91) as applied to claim above, and further in view of Leung et al (int. J. Cancer 60:534-538, 1995, IDS #5) and Qu et al (Glycobiology 7:803-809, 9/97, IDS #5).

The claims recite a glycosylated antibody with a reactive ketone group or an immunoconjugate conjugated through a reactive ketone wherein the glycosylated site is Vκ-N , HCN1, or HCN5 or more than one of these sites, wherein the conjugate is a toxin or drug.

Shih et al teach oxidizing a carbohydrate of an antibody to produce ketones and conjugating drugs and toxins to the oxidized antibody (see column 2, lines 34-42). Shih et al does not teach glycosylation at the HCN1, HCN5, or Vκ-N site. These deficiencies are made up for by the teachings of Leung et al ans Qu et al.

Leung et al teach a glycosylation site in the Vκ domain at residues 18-20 in an inmmunoglobulin and this site can be used for drug or radionuclide conjugations (see page 534).

Qu et al teach antibodies engineered to contain a glycosylation site at HCN1 and HCN5 and conjugates comprising such (see abstract and page 803).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have engineered a glycosylation site in the HCN1, HCN5, and Vκ-N sites in an antibody as taught by Qu et al and Leung et al and conjugate a toxin or drug to the ketone group on the as taught by Shih et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have engineered a glycosylation site in the HCN1, HCN5, and Vκ-N sites in an antibody as taught by Qu et al and Leung et al and conjugate a toxin or drug to the ketone group on the as taught by Shih et al because Shih et al teach a method of conjugation to any glycosylated site in an antibody by oxidizing the carbohydrate to ketone groups. In addition,

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have engineered a glycosylation site in the HCN1, HCN5, and Vκ-N sites in an antibody as taught by Qu et al and Leung et al and conjugate a toxin or drug to the ketone group on the as taught by Shih et al because Leung et al and Qu et al teach glycosylation sites which do not interfere with antigen binding and Qu et al teach that the mutant antibodies show superior coupling efficiencies with no adverse effects on immunoreactivities (see page 803 in Leung et al).

Claim 55 is directed to an antibody prepared by the method of claim 1. Applicant is reminded that when the claim is directed to a product, the preamble is generally nonlimiting if the body of the claim is directed to an old composition and the preamble merely recites a property inherent in the old composition. [*Kropa v. Robie*, 88 USPQ 478, 480 - 81 (CCPA 1951); see also MPEP 2111.02.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusions

17. No Claims are allowed.

18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

20. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

Sheela J. Huff

SHEELA HUFF
PRIMARY EXAMINER